Remarks

Claims 1-8 were initially pending in the subject application. In response to a restriction requirement, claims 1-6 were elected for examination on July 10, 2003. By way of the amendment of this date, claims 2 and 4-8 have been canceled and claims 9-16 have been added. Therefore, claims 1, 3, and 9-16 are now before the Examiner for consideration. The subject invention provides unique and advantageous methods for the prediction of the responsiveness of patients to beta-blocker medications comprising the genotyping of the β_1 adrenergic receptor of the patient, wherein the presence of a homozygous Ser49 phenotype or the Ser49/Arg389 phenotype is indicative of a likely response to beta-blocker medications. Certain of the claims have been amended for the purpose of expediting the patent application process in a manner consistent with the Patent and Trademark Office Patent Business Goals (PBG), 65 Fed. Reg. 54603 (September 8, 2000), in order to correct antecedent basis issues the claimed subject matter, advance prosecution, and facilitate the business interests of Applicant(s). Support for these new claims and the amendments to the pending claims can be found throughout the subject specification, including, for example, the claims as originally filed, paragraph 23, and Example 4, page 12. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Claims 1, 2, 4, and 5 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Maqbool *et al.* The Office Action argues that Maqbool teaches a method of screening for β_1 adrenoreceptor polymorphisms comprising genotyping the receptor of an individual at codons 49 and 389. The Office action also indicates that the reference suggests, but does not teach that the presence of the polymorphisms are indicative of a likely response to beta blocker medications. The Office Action then indicates that it would have been prima facie obvious to one skilled in the art to genotype the polymorphisms in order to analyze their effect on treatment. Claims 4 and 6 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Mason *et al.* The Office Action argues that Mason teaches a method of screening for β_1 adrenoreceptor polymorphisms comprising genotyping the receptor of an individual at codon 389. The Office action also indicates that the reference suggests, but does not teach that the presence of the polymorphism is indicative of a likely

response to beta blocker medications. The Office Action then indicates that it would have been prima facie obvious to one skilled in the art to genotype the polymorphism in order to analyze its effect on treatment. Claims 1-6 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Maqbool *et al.* in view of Mason *et al.* The Office Action argues that Maqbool teaches a method of screening for β_1 adrenoreceptor polymorphisms comprising genotyping the receptor of an individual at codons 49 and 389. The Office Action indicates that Maqbool fails to teach the specific beta blockers of claims 3 and 6 and that Maqbool does not directly predict the effects of the polymorphisms on responsiveness to beta blocker medications. The Office Action further indicates that Mason suggests, but does not teach that the presence of the polymorphisms are indicative of a likely response to beta blocker medications. The Office Action then indicates that it would have been prima facie obvious to one skilled in the art to genotype the polymorphism in order to analyze its effect on treatment and that Mason expressly predicts and teaches the effect of the codon 389 polymorphism and suggests determining the effect of the different antagonists on the gene variants, which is an express suggestion that some variants are more likely than others to respond to beta blockers. Thus, an ordinary practitioner would have expected differential effects of beta blockers at these two positions. Applicants respectfully traverse each of the rejections.

Applicants respectfully submit that the subject invention is not rendered obvious by the teachings of Maqbool *et al.* alone, Mason *et al.* alone, or the combination of Maqbool *et al.* in view of Mason *et al.* As the Patent Office is aware, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). In the case of the instant invention, it is respectfully submitted that the cited references, wither alone or in combination, fail to teach or render obvious the claimed invention. For example, the cited references fail to teach that the presence of both the Ser49 and Arg389 phenotypes are indicative of a likely response to beta-blocker medications. Additionally, the references fail to teach or suggest that individual homozygous for the presence of Arg389 and/or Ser49 are likely to be responsive to bet-blocker medications. Indeed, both Maqbool *et al.* and Mason *et al.* are silent with respect to the existence of Ser49 and Arg389 homozygotes. Applicants also respectfully submit indicate that the references, alone or in combination, also fail to render a method of treating hypertension comprising

the steps of genotyping the β_1 adrenergic receptor of an individual at codons 49 and 389 and prescribing beta-blocker medication to said individual when the individual is homozygous for the Ser49 phenotype or has a Ser49/Arg389 phenotype. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Furthermore, a determination of obviousness not only requires that the prior art would have suggested the claimed process to one of ordinary skill in the art, but also that the process would have a reasonable likelihood of success when viewed in light of the prior art. *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). A rejection based on a reference or a combination of references amounts to an "invitation to experiment" and is thus "obvious-to-try," when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result or that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990). It is respectfully submitted that the rejections of record amount to an invitation to experiment on the part of the skilled artisan; accordingly, reconsideration and withdrawal of the rejections of record is respectfully requested.

Applicants further submit that the references, either alone or in combination, further fail to render the claimed invention obvious with respect to individuals homozygous for Arg389 and that those individuals exhibiting the Ser49/Arg389 haplotype pair exhibited an unexpectedly significant response to beta-blocker therapy as compared to individuals exhibiting a Gly49/Arg389 or Ser49Gly389 haplotype pair. As is indicated in Johnson *et al.* (Clinical Pharmacology & Therapeutics (74(1): 44-52, 2003), patients homozygous for Arg389 has a nearly 3-fold greater reduction in diastolic blood pressure as compared to those carrying the variant allele. Additionally, patients having the Ser49Arg389/Ser49/Arg389 diplotype exhibited a decline in blood pressure of 14.7mm Hg as compared to 0.5 mm Hg for patients with the Gly49Arg389/Ser49Gly389 diplotype (see page 44, "Results:"). As further indicated in the reference, codon 389 and codon 49 genotypes were significant predictors of responsiveness to blood pressure medications. It is respectfully submitted that Maqbool *et al.* and/or Mason *et al.* fail to teach, suggest, or render obvious methods

that utilize both the Ser49 and Arg 389 alleles as the combination of these alleles provides an unexpectedly better association of responsiveness to hypertension medications than do either of the alleles alone. Accordingly, reconsideration and withdrawal of the rejections is respectfully requested.

In view of the foregoing remarks and the amendments to the claims, the applicant believes that the pending claims are now in condition for allowance, and such action is respectfully requested. The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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FCE/mv
Attachments: Petition and Fee for Extension of Time
Johnson *et al.* (2003)

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